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Epitranscriptomics of cancer

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Epitranscriptomics of cancer

Marina Tusup, Thomas Kundig, Steve Pascolo

Marina Tusup, Thomas Kundig, Steve Pascolo, Department of Dermatology, University Hospital of Zürich, Zurich 8091, Switzerland

Marina Tusup, Thomas Kundig, Steve Pascolo, Faculty of Medicine, University of Zurich, Zurich 8091, Switzerland

ORCID number: Marina Tusup (0000-0001-7746-1057); Thomas Kundig (0000-0003-3863-8766); Steve Pascolo (0000-0003-2946-5576).

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Correspondence to: Steve Pascolo, PhD, Senior Scientist, Department of Dermatology, University Hospital of Zürich, Gloriastrasse 31, Zurich 8091, Switzerland. steve.pascolo@usz.ch
Telephone: +41-44-6342877
Fax: +41-44 6342872

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Abstract

The functional impact of modifications of cellular RNAs, including mRNAs, miRNAs and lncRNAs, is a field of intense study. The role of such modifications in cancer has started to be elucidated. Diverse and sometimes opposite effects of RNA modifications have been reported. Some RNA modifications promote, while others decrease the growth and invasiveness of cancer. The present manuscript reviews the current knowledge on the potential impacts of N6-Methyladenosine, Pseudouridine, Inosine, 2'O-methylation or methylcytidine in cancer's RNA. It also highlights the remaining questions and provides hints on research avenues and potential therapeutic applications, whereby modulating dynamic RNA modifications may be a new method to treat cancer.

Key words: RNA modifications; N6-methyladenosine; 5-methylcytidine; 2'O-methylation or methylcytidine; Pseudouridine; Inosine

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Core tip: The present manuscript reviews the current knowledge on RNA modifications in cancer. The potential impacts of N6-Methyladenosine, Pseudouridine, Inosine, 2'O-methylation or methylcytidine in cancer's RNA is presented and discussed. The review also highlights the remaining questions and provides hints on research avenues and potential therapeutic applications, whereby modulating dynamic RNA modifications may be a new method to treat cancer.

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INTRODUCTION

Diverse and abundant modifications are introduced

posttranscriptionally in cellular RNAs during their maturation. These modifications are made on canonical A, C, G, and U residues, and their formation is catalyzed by numerous specific enzymes or RNA-protein complexes (RNPs). Ribonucleotide residues can bear single or multiple modifications on the purine/pyrimidine ring and/or ribose. To date, over one hundred RNA modifications have been identified and listed in dedicated databases (<http://mods.ma.albany.edu/>; <http://modomics.genesilico.pl>)^[1,2]. These naturally occurring modified nucleosides play various structural and functional roles in different types of RNAs: Transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), messenger RNAs (mRNAs), small nuclear RNAs (snRNAs), microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). The most widespread RNA modifications are base or ribose methylations, deamination of adenosine to inosine and isomerization of uridine into pseudouridine. Over the past decades these modifications have been studied in the context of malignancies. Frequently, a modification is found to have pro-cancer or anti-cancer effects depending on the type of RNA, the location of the modification and, most importantly, the cell type and context (*e.g.*, hypoxia). This review presents the current knowledge on the potential link between RNA modifications and cancer by systematically addressing the “pro-cancer”, “anti-cancer” and mixed effects of RNA modifications. Since such a relationship has been reported for only some abundant modifications and for modifications for which a detection method is available [N⁶-Methyladenosine (m⁶A), 5-Methylcytidine (m⁵C), 2'-O-mN, Ψ and I], the present review will focus on these modifications (Figure 1).

M6A IN CANCER RNA

Serendipitously discovered during the characterization of the mRNA 5' cap, methylation of the exocyclic nitrogen of adenosine, named m⁶A, is by far the most abundant mRNA modification, occurring on an average of three sites per mRNA^[3-5]. Recent technological advances have facilitated m⁶A profiling across eukaryotes, including humans, mice^[6], yeasts^[7], and plants^[8,9], indicating that m⁶A is a conserved but dynamic modification. m⁶A has also been identified in rRNA^[10], tRNA^[11], snRNA^[12], miRNA^[13] and lncRNA^[14].

M⁶A patterns are attributed to the consensus RR-ACH sequence (A is methylated; R = A or G; H = A, C, or U; and the first nucleotide next to m⁶A from the 5' end most frequently is G), with preferential distribution near mRNA stop codons and 3' untranslated regions (UTRs) and within long internal exons. Additionally, the m⁶A sites are conserved between human and mouse embryonic stem cells (ESCs) and somatic cells. However, distinct m⁶A patterns can also be detected among different species or cells at different developmental stages^[4,7,15,16]. Some m⁶A signatures are tissue specific^[4], and are altered in response to different stimuli^[17], pointing to the potential role of m⁶A in regulating diverse

cellular processes. m⁶A dynamics are assigned to the complex m⁶A enzymatic machineries, comprising m⁶A “writers”, “readers” and “erasers”. Although a plethora of studies suggest crucial and versatile roles of m⁶A and its machineries, its roles in cancer that have recently emerged are contradictory and require further investigation.

High m⁶A levels in cancers

“Writers” is a term given to enzymes that are part of the methyltransferase complex that introduces m⁶A. Components of this complex are methyltransferase-like 3 (METTL3)^[18], METTL14^[19], Wilms tumor 1-associated protein (WTAP)^[20] and KIAA1429^[21].

METTL3 protein levels were found to be elevated in lung adenocarcinoma cell lines compared to healthy tissue^[22]. Depletion of METTL3 was shown to result in the inhibition of cancer cell growth, decreased invasive ability of cancer cells and increased cell apoptosis in the same study. Additionally, METTL3 was shown to function as an m⁶A-binding protein (“reader”) in a specific subset of m⁶A-modified mRNAs, where it recruits eIF3 during translation initiation and therefore promotes translation. Expression of several oncogenes, including the mRNA of epidermal growth factor receptor (EGFR) and the Hippo pathway effector transcriptional co-activator with the PDZ-binding motif (TAZ) protein, was found to be promoted upon METTL3 recognition^[22].

Similarly, in acute myeloid leukemia (AML), mRNA levels of METTL3 and METTL14 are significantly higher than in most cancers^[23]. METTL3 depletion in MOLM13 caused differentiation and increased apoptosis, suggesting that high m⁶A levels may play a role in sustaining undifferentiated leukemic cells in AML^[23] (Table 1).

Low m⁶A levels in cancers

Two m⁶A “erasers” have been described: Demethylases fat mass and obesity-associated protein (FTO) and alkB homolog 5 (ALKBH5)^[24,25].

Single nucleotide polymorphisms within FTO known to be involved in the development of obesity in genome-wide association studies have been associated with the risk of developing diverse cancer types: Lung cancer, kidney cancer, high-grade prostate cancer, endometrial cancer, pancreatic cancer, pancreatic cancer in patients with type 2 diabetes, and breast cancer^[26-33]. All these cancer types share a single SNP (rsrs9939609): The obesity-associated SNP in intron 1 of the *FTO* gene. This SNP was shown to increase primary transcript levels of the *FTO* gene, suggesting a gain-of-function mutation in cancers associated with this SNP^[34].

In human epidermal growth factor receptor type 2 (HER2)-overexpressing subtypes of breast cancer, FTO is highly expressed in comparison to other breast cancer subtypes^[35]. Contrary to the studies of high m⁶A levels in AML discussed in the previous chapter, low m⁶A levels have also been reported in AML subtypes. FTO expression can be upregulated by certain

Table 1 Relative amount of modification (directly quantified or extrapolated from the expression level of writers/erasers)

RNA modifications	High in cancer	Low in cancer
m6A	Lung adenocarcinoma ^[22] , AML ^[23]	HER2 overexpressing subtypes breast cancer ^[35] , t(11q23)/MLL-rearranged, t(15;17)/PML-RARA, FLT3-ITD, and/or NPM1-mutated AMLs (ASB2 and RARA) ^[36] , GBM (FOXM1) ^[39] , breast cancer (NANOG) ^[40]
2'O-methylation	Breast cancer ^[51,67] , primary and metastatic prostate cancers ^[58] , squamous cell cervical carcinoma ^[57]	
Ψ		Leukemia, lymphoma, multiple myeloma ^[84-86]
Inosine	BLCA, BRCA, COAD, HNSC, LUAD, THCA ^[87,88] , NSCLC (NEIL1 ^[94] , AZIN1 ^[103] , miR-381 ^[94]), SCLC (AZIN1 ^[87] , HCC (AZIN1 ^[101] , FLNB ^[90]), GC ^[91] , ESCC (FLNB ^[92] , cervical cancer ^[89] , CRC (RHOQ) ^[109] , AML (PTPN6) ^[114]	KIRP, KICH ^[87,88] , Breast cancer (Gabra3) ^[118] , Gastric cancer (PODXL) ^[91] , Glioblastoma (GluR-B) ^[119] , onco miR-21, miR-221, miR-222 ^[128] , ESCC (IGFBP7) ^[120] , Glioma (miR-376a*) ^[129] , Melanoma ^[130] (miR-455-5p) ^[132]
5mC	Circulating tumor cells in lung cancer ^[137]	

In brackets are the names of genes that have been analyzed. AZIN1: Antizyme inhibitor 1; RHOQ: Ras homolog family member Q; PODXL: Podocalyxin-like; IGFBP7: Insulin-like growth factor-binding protein 7; PTPN6: Protein tyrosine phosphatase non-receptor type 6; NEIL1: NEI-like protein 1; GluR-B: Glutamate R-B; Gabra3: Alpha-3 subunit of gamma-aminobutyric acid type A; FlnB: Filamin B; ASB2: Ankyrin repeat and SOCS box containing 2; RARA: Retinoic acid receptor alpha; FOXM1: Forkhead box protein M1; GBM: Glioblastoma multiforme; HER2: Human epidermal growth factor receptor type 2; MLL: Mixed lineage leukemia; PML/RARA: Promyelocytic leukemia/retinoic acid receptor alpha; FLT3-ITD: Fms-related tyrosine kinase 3-internal tandem duplication; NPM1: Nucleophosmin 1; NSCLC: Non-small cell lung cancer; HCC: Hepatocellular carcinoma; ESCC: Esophageal cell carcinoma; GC: Gastric cancer; CRC: Colorectal cancer; AML: Acute myeloid leukemia; SCLC: Small cell lung cancer; BLCA: Bladder urothelial carcinoma; BRCA: Breast invasive carcinoma; COAD: Colon adenocarcinoma; HNSC: Head and neck squamous cell carcinoma; LUAD: Lung adenocarcinoma; THCA: Thyroid carcinoma; KICH: Kidney chromophobe; KIRP: Kidney renal papillary cell carcinoma.

oncogenic proteins (e.g., mixed lineage leukemia (MLL)-fusion proteins, promyelocytic leukemia/retinoic acid receptor alpha (PML-RARA), fms-related tyrosine kinase 3-internal tandem duplication (FLT3-ITD), and nucleophosmin 1 (NPM1) mutant), and dataset analysis of human AML confirmed that FTO was expressed at significantly high levels in t(11q23)/MLL-rearranged, t(15;17)/PML-RARA, FLT3-ITD, and/or NPM1-mutated AMLs^[36]. Overexpression of FTO reduces m6A levels in ankyrin repeat and SOCS box containing 2 (ASB2) and retinoic acid receptor alpha (RARA) mRNA transcripts. It has been shown that the loss of m6A markings reduces mRNA stability, resulting in the partial repression of ASB2 and RARA expression in AML cells. In four different AML cohorts, ASB2 and RARA exhibit a significant inverse correlation with FTO expression. ASB2 and RARA are upregulated during normal hematopoiesis and are important regulators of all-*trans*-retinoic acid (ATRA)-induced differentiation of leukemia cells. Through regulating the expression of such targets, FTO inhibits ATRA-induced AML cell differentiation. Both gain- and loss-of-function studies of FTO in leukemic cell models showed an oncogenic role of FTO in these AML subtypes^[36]. However, recent studies have suggested that FTO acts as a demethylase of N6-2' O-dimethyladenosine in mRNA 5' caps, having only minor effects on m6A^[37]. Thus, the role of FTO in AML might be independent of m6A.

Recently, both FTO and ALKBH5 have been found to play similar roles in glioblastoma stem cells (GSCs) and their tumorigenesis^[38]. These studies shed light on their crucial roles in the regulation of mRNA m6A levels for maintaining GSC growth, self-renewal, and tumor development. Enhanced growth and self-renewal of GSCs *in vitro* were detected upon the depletion of

METTL3 or METTL14, resulting in reduced mRNA m6A levels, and promoted the ability of GSCs to form brain tumors *in vivo*. Accordingly, treatment with the FTO inhibitor MA2, the ethyl ester form of meclofenamic acid, increased mRNA m6A levels and suppressed GSC growth *in vitro* and GSC-initiated tumorigenesis, ultimately prolonging the survival of GSC-engrafted mice.

In a similar study, the authors checked the expression levels of m6A regulators in available datasets for glioblastoma multiforme (GBM) and discovered elevated expression of m6A demethylase ALKBH5 that correlated with poor clinical outcomes for GBM patients^[39]. Stable knockdowns in cultured human GSCs showed that the loss of ALKBH5 decreases GSC proliferation and reduces the expression of the stemness markers Nestin, Sox2, Nanog, and Oct4, which are normally expressed in GSCs. In rescue experiments, wild-type, but not catalytically inactive, ALKBH5 recover the phenotype, suggesting that it plays a role in stemness maintenance and that the proliferation of GSCs is solely based on demethylation activity. Moreover, these authors examined the expression of transcription factor FOXM1 (forkhead box m1), which is known to play a pivotal role in regulating GSC proliferation, self-renewal, and tumorigenicity, and found that it depends on ALKBH5 demethylating activity. All these findings were based on m6A hyper erasing, which opens new possibilities for promising targeted treatments in glioblastoma (Table 1).

It has been reported that the hypoxia-inducible factors (HIFs) HIF-1 α and HIF-2 α activate *ALKBH5* gene transcription under hypoxic conditions in breast cancer cells, thus inducing m6A demethylation. This demethylation was shown to stabilize NANOG mRNA and promote the breast cancer stem cell (BCSC)

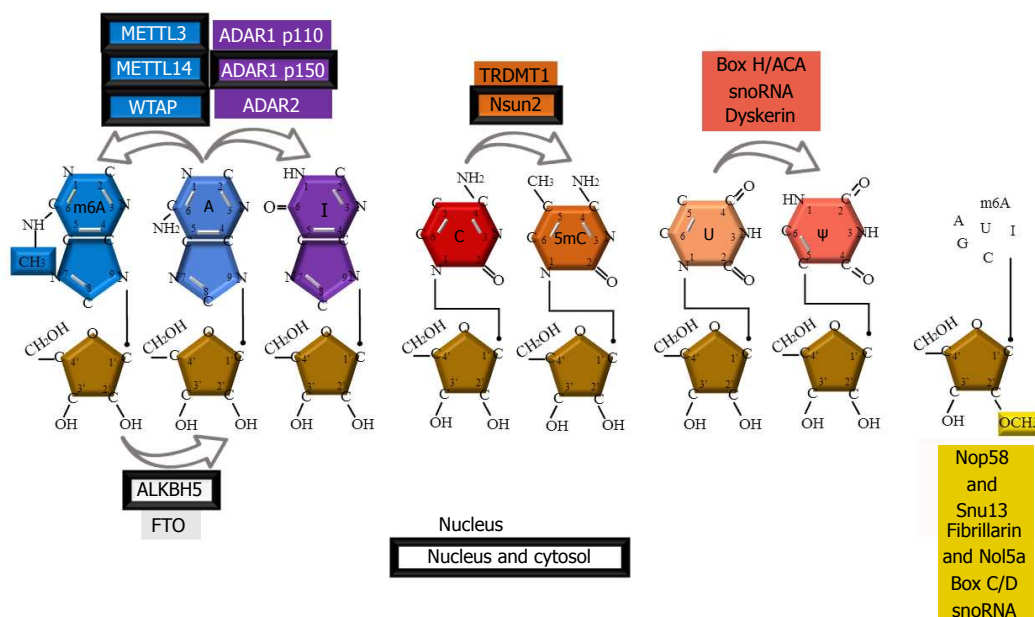


Figure 1 Ribonucleotide RNA modifications known to be of relevance in cancer and their enzymatic machineries. m6A: N6-methyladenosine; METTL3: Methyltransferase like 3; METTL14: Methyltransferase like 14; WTAP: Wilms' tumor 1-associating protein; m6A erasers (ALKBH5: Alkylation repair homologue protein 5; FTO: Fat mass and obesity-associated protein); Inosine (I) writers [ADAR1 (p110 and p150) and ADAR2: Adenosine deaminase acting on RNA 1 and 2]; 5-methylcytosine (5mC) (NSUN2: NOP2/Sun domain protein 2; TRDMT1: tRNA aspartic acid MTase 1); 2'-O-methylation writers (Nol5a: Nucleolar Protein 5A; Nop58: Nucleolar protein 58; Snu13: Small Nuclear Ribonucleoprotein 13; SnoRNA: Small nucleolar RNA).

phenotype. Depletion of ALKBH5 in hypoxic breast cancer cells was identified as an effective strategy to decrease NANOG expression and limit the presence of BCSCs *in vivo*^[40] (Table 1).

Mixed role of m6A in cancer

The primary microRNA (pri-miRNA) junction region between the hairpin stem and the flanking single-stranded RNA was found to be abundant in m6A consensus motifs. The recognition of the junction regions is mediated by Dicer, followed by the recruitment of the ribonuclease Drosha (the microprocessor complex), which cleaves the RNA duplex to yield the premiRNA product. Depletion of HNRNPA2B1 (a nuclear "reader") or METTL3 knockdown in HEK293 and MDA-MB-231 cells resulted in a significant reduction in the expression levels of the mature forms of a number of m6A-marked miRNAs. The tumor-suppressor miRNA let-7 was significantly reduced upon the depletion of METTL3 possibly due to diminished Dicer binding to pri-miRNAs, thus preventing the formation of mature miRNAs. However, these METTL3-depletion experiments also showed a decrease in the expression of onco-miRNAs, such as miR-221 and miR-222^[13,41]. Taken together, the presence of m6A affects diverse pri-miRNA and mature miRNA subpopulations, but its relevance in the context of cancer still needs to be investigated.

2'-O-METHYLATION IN CANCER RNA

Methylation of the 2'-hydroxyl group of ribose is one of the predominant internal modifications of rRNA and

snRNA^[10,42]. This modification is also found in tRNA and mRNA, mostly at the first and second nucleotides in Cap1 and Cap2 structures, respectively.

Introducing 2'-O-methylation on ribose is mediated by complexes of guide RNA and proteins named small nucleolar ribonucleoprotein (snoRNP) complexes or by methyltransferases: Human cap1 and 2, 2'-O-ribose methyltransferase, hMTr1 and hMTr2^[43-45]. snoRNP complexes consist of Fibrillarin (the catalytic component in humans, also known as Nop1p in yeast), Nol5a (Nop56p), Nop58 and Snu13 subunits^[46-48], which are guided by C/D Box snoRNAs to the appropriate base^[49,50].

High 2'-O-methylation levels in cancer

Tumor suppressor p53 and Fibrillarin seem to be linked^[51]. Knockdown of p53 in cellular models of breast and colon cancer resulted in the overexpression of Fibrillarin at both the mRNA and protein levels. It is suggested that tumorigenesis associated to mutated p53 promotes an increase in the methylation status of rRNAs, which alters their ribozyme activity, thus affecting their translation fidelity and rate. Through the methylation of rRNA, Fibrillarin stimulates the translation of cancer-promoting proteins: (1) Insulin-like growth factor 1 receptor (IGF1R), which plays a role in tumor progression, cell survival, and the response to chemotherapy (reviewed by Pollak *et al.*^[52]); (2) c-Myc, a pleiotropic pro-oncogene (reviewed by Dang *et al.*^[53]); (3) Fibroblast growth factor 1/2 (FGF1/2), which is involved in epithelial-mesenchymal transition^[54]; and (4) Vascular endothelial growth factor

A (VEGFA), which acts in tumoral angiogenesis^[51,55].

Translation of these proteins relies on internal ribosome entry site (IRES) in the mRNA, which is a 5' cap-independent translation mechanism that may be used in specific conditions. The inhibition of rRNA methylation was shown to impair IRES translation initiation by perturbing the association of the 40S and 60S subunits^[56]. Therefore, it is conceivable that enhanced ribosomal methylation increases the translation of IRES-containing mRNAs. Nevertheless, clinical analysis shows that a high level of Fibrillarin in primary breast tumors is associated with poor survival, independent of other biological markers^[51]. Elevated expression levels of Fibrillarin were previously reported in primary and metastatic prostate cancers and in squamous cell cervical carcinoma (Table 1)^[57,58].

NOL5A gene was found to be overexpressed in Burkitt's lymphoma-associated c-Myc mutants^[59], and human NOP58 mRNA levels were found to be elevated in metastatic melanoma lesions^[60].

Low 2'O-methylation levels in cancer

Contrary to Fibrillarin's indirect promotion of IRES-driven translation, in MCF-7, a breast cancer cell line, Fibrillarin knockdown resulted in the accumulation of p53, possibly affecting the UTR of the p53 mRNA and increasing IRES-driven *de novo* synthesis^[61]. These studies suggest a complex interplay between p53 and Fibrillarin, while IRES-dependent translation is not exclusively stimulated by increased rRNA methylation.

Mixed 2'O-methylation in cancer

SnoRNA expression profiles were investigated in endometrial, lung and prostate cancers, as well as in glioma and chronic lymphocytic leukemia. High-throughput screening of snoRNAs in cancerous versus normal tissues underlined their overexpression or underexpression as common molecular events in tumorigenesis, with the former being more pronounced than the latter^[62-66]. Analysis of blood serum has shown the possibility of detecting snoRNAs in breast cancer patient samples and the associated upregulation of a specific snoRNA, U6, in active disease^[67]. Therefore, profiling snoRNAs with their respective RNA 2'O methylation modification signatures might be used as a noninvasive biomarker in the diagnosis and prognosis of cancer.

PEUDOURIDINE IN CANCER RNA

The fifth base, known as pseudouridine (Ψ)^[68], is one of the most abundant nucleotide modifications present in all three life domains^[2]. After its initial detection in rRNA and tRNA, pseudouridine was detected in mRNA, lncRNA, and snRNAs, such as U2 snRNA and snoRNA^[69,70]. Introducing Ψ in eukaryotic RNA can be mediated through guide RNA-dependent H/ACA BOX snoRNA pseudouridine synthases (PUSs) or guide RNA-independent PUSs. A recent review by Penzo *et al.*^[71] reports on the functional roles of pseudouridines and related human pathologies.

Only low Ψ levels have been reported in cancer tissues/cells; thus, this chapter will contain only a section titled "low Ψ levels in cancer". Surprisingly, elevated levels of circulating Ψ have been measured in the body fluids of cancer patients, but its role and origin are not well defined, so this finding will not be further discussed here.

Low Ψ levels in cancer

The highly conserved protein dyskerin is the human PUS that catalyzes the pseudouridylation of snoRNPs that assemble during the transcription of guide H/ACA RNA. Mutations in the *Dkc1* gene coding for dyskerin can be found in the X-linked form of dyskeratosis congenita (DC). DC is a rare, inherited disorder that is characterized by mucocutaneous abnormalities and bone marrow failure. DC can be inherited as an X-linked recessive, autosomal dominant or autosomal recessive disease^[72]. Although the absence of dyskerin, which results in the loss of pseudouridine in rRNA, was suggested as a primary cause of DC, a recent study assigned telomerase dysfunction as the primary cause of DC^[73]. Namely, mutations in H/ACA-resembling domains in the RNA component of telomerase RNP, which are required for telomerase accumulation, stability, 3' end processing and function, are associated with an autosomal form of DC^[74-76].

In patients with DC, a higher predisposition to cancer has been reported, although low mutational frequency in the *DKC1* gene was shown in primary tumors^[77]. This predisposition might be a synergistic outcome of impaired pseudouridylation. Most likely, the dysregulation of rRNA pseudouridylation precedes disease onset, as studies in hypomorphic *Dkc1*-mutant mice suggest. A specific defect of the internal ribosome entry site also occurs upon *DKC1* loss, causing a specific defect in the translation of some IRES-containing mRNAs. Ribosomes that lack pseudouridine modifications show a direct impairment in binding to IRES elements^[78]. Consequently, in hypomorphic *DKC1* mice, cap-dependent translation of mRNA is not compromised, but translation of IRES-containing mRNAs, including the tumor suppressors p27 and p53, is perturbed^[79-82], resulting in a higher incidence of cancer development in these mice. Thus, this impaired translation of tumor suppressor mRNA might also be a driver of cancer in DC patients. Moreover, recent identification of Ψ in mRNA^[83] brings an additional level of complexity and regulation of the expression of target RNAs.

In hematological cancers, such as leukemias, lymphoma and multiple myeloma, downregulation of specific subsets of dyskerin-associated H/ACA snoRNAs has been demonstrated^[84-86] (Table 1). Thus, lower pseudouridylation levels are a widespread feature of cancer.

INOSINE IN CANCER RNA

Inosine is an RNA modification resulting from the hydrolytic deamination of adenosine catalyzed by adenosine

deaminase enzymes acting on double-stranded RNA (ADAR) or adenosine deaminase acting on transfer RNA (ADAT), which are families known to function in A-to-I RNA editing. Enzymes of the ADAR family are catalytically active ADAR1, ADAR2 and ADAR3, which still has an unknown function.

ADARs introduce inosine in coding and non-coding RNAs and have drastic impacts on the cellular transcriptome and translome. The hypo- or hyper-editome has been associated with diverse types of cancer. The role of ADAT in cancer has not been reported.

High editing levels in cancer

Most frequently editing locations are long, partially complementary RNAs formed from inverted non-coding repeats, such as *Arthrobacter luteus* (Alu) and long interspersed element (LINE) located in mRNA UTRs and introns. Two major studies have investigated RNA-editing patterns in tumors versus normal tissues. Each of the studies employed RNA-Seq datasets from The Cancer Genome Atlas (TCGA) project (<https://cancergenome.nih.gov/>) and compared them to reference datasets of editing sites. High-confidence RNA editing sites are annotated in the Rigorously Annotated Database of A-to-I RNA Editing (RADAR, <http://rnaedit.com/>), where one study focused on detecting Alu and non-Alu RNA editing events in 17 cancers, whereas the other study focused on Alu RNA editing events in 9 different cancers^[87,88].

In general, elevated Alu editing activity in tumors compared to matched normal tissues was found in bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), colon adenocarcinoma (COAD), head and neck squamous cell carcinoma (HNSC), lung adenocarcinoma (LUAD) and thyroid carcinoma (THCA). This hyperediting of Alu was attributed to ADAR1, whose expression levels matched in all these types of cancer, except COAD. Similarly, a study by Han *et al.*^[87] where more patient samples and non-Alu edited sequences were included, confirmed hyperediting in BLCA, BRCA, HNSC, LUAD, THCA compared to normal tissues. Again, increased editing levels correlated with the mRNA levels of ADAR1.

Increased ADAR-1 levels were reported in non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), esophageal cell carcinoma (ESCC), gastric (GC) and cervical cancer, suggesting that tight regulation of editing levels might have implications in cancer development and that ADAR1 might act as an oncogene^[89-92] (Table 1 and Figure 2).

Recoding editing: In non-small cell lung cancer samples, *ADAR1* gene amplification was shown to increase the editing of the DNA base excision repair glycosylase enzyme NEI-like protein 1 (NEIL1). Pre-mRNA editing of NEIL-1 causes a lysine to arginine (K242R) change in the lesion recognition loop of the protein. The edited NEIL1 protein removes thymine glycol from duplex DNA at a lower rate compared to the unedited form, while

repair of the guanidinohydantoin lesion is enhanced by edited NEIL1^[93]. In overexpression experiments, transfection of edited NEIL1 enhanced the growth of A459 cells in comparison with the transfection of unedited transcripts. Thus, increased recoding editing of NEIL1 as a proposed target of ADAR1 could contribute to the phenotype of lung cancer cells^[94].

AZIN1 (encoding antizyme inhibitor 1) is edited by ADAR1, which has increased expression levels in HCC and was found to positively correlate with AZIN1 editing frequency. AZIN1 is an antizyme inhibitor whose activity is crucial in limiting cellular proliferation. Antizyme binds and induces the degradation of the growth-promoting proteins ornithine decarboxylase (ODC) and cyclin D1 (CCND1)^[95,96]. AZIN1 is homologous to ODC and has a greater binding affinity to antizyme compared to ODC. Binding of AZIN1 to antizyme prevents the degradation of ODC^[97]. Thereby, AZIN1 acts as an oncogene by inhibiting the tumor-suppressor activities of antizyme^[96]. AZIN1 expression was found to be substantially elevated in cancers of the prostate, brain, breast and liver, and gene expression data have identified alterations in the AZIN1-to-antizyme ratio in many human cancers, confirming its role in promoting growth^[98-100]. In HCC, increased A-I editing of the AZIN1 transcript introduces serine-to-glycine substitution at residue 367 in the protein. This recoding editing is associated with conformational changes and translocation from the nucleus to the cytoplasm and results in a higher-binding affinity to antizyme and greater protein stability, thus promoting cell proliferation. AZIN1 editing increases during the progression from primary liver cancer and cirrhosis to advanced HCC with recurrence and metastasis, suggesting its use as a prognostic marker^[101]. It is plausible that similar editing events occur in other types of cancer, as has been confirmed in esophageal squamous cell carcinoma (ESCC) and breast cancer^[87,92,102]. Recently, tumorigenesis of NSCLC was also attributed to high levels of AZIN1 editing^[103]. It has been reported that AZIN1 editing levels correlate with sensitivity to drug treatment in cancer cell lines. Cancer cells lines with increased levels of AZIN1 editing showed more sensitivity to some of the chemotherapies used in small cell lung cancer (SCLC): Paclitaxel, irinotecan, and topotecan^[87].

Filamin B (FLNB) is an actin cross-linking protein and, together with filamin A, it forms homo- and heterodimers mediating orthogonal branching of actin filaments^[104]. Filamin B is known to be a target for editing^[105], and interestingly, one recoding editing event was shown to be increased in two types of cancer. In HCC, ADAR1 and ADAR2 were both reported to mediate FLNB transcript editing in codon 2269, resulting in the amino acid change Met→Val. Increased editing of FLNB compared to matched non-tumor liver tissues has been closely associated with HCC pathogenesis from normal to clinically verified HCC. In this study, ADAR1 levels were shown to be increased, while ADAR2 levels were decreased in HCC samples compared to non-tumor

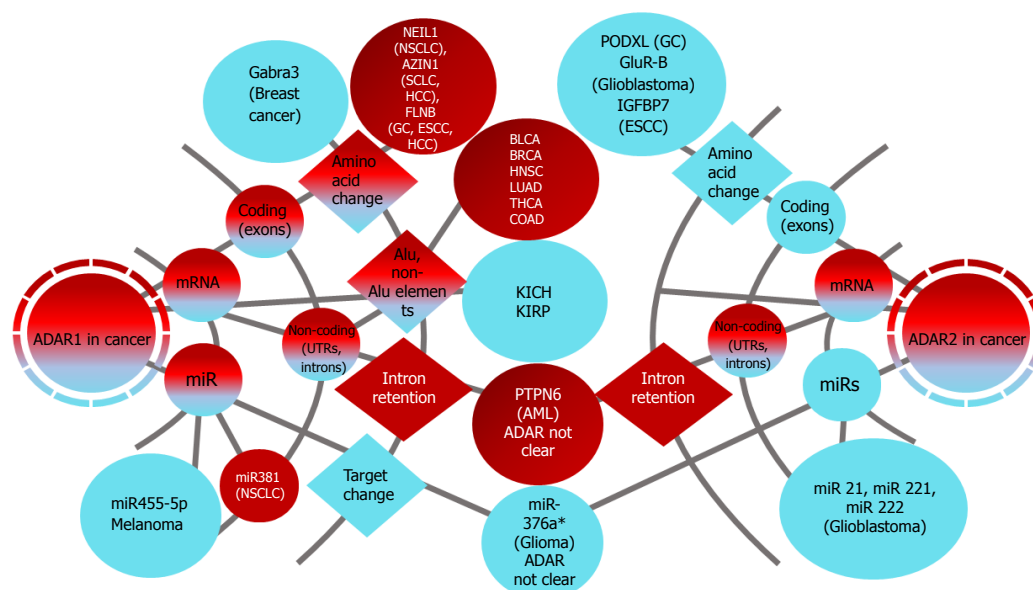


Figure 2 Editing of double-stranded RNA on mRNA and miRNA. Below, high ADAR1 levels are associated with breast cancer, NSCLC, colon cancer and cervical cancer, while low ADAR1 levels are shown in melanoma. Low levels of ADAR2 are present in glioblastoma. HCC, ESCC and gastric cancer are indicated as ADAR2-low and ADAR1-high cancers. The potential roles of ADAR1 and ADAR2 in cancer are depicted by mind map. Red means high expression/inosine content and blue means low expression/inosine content. In circles are the names of molecules/cancers and in diamonds are the mechanisms. NSCLC: Non-small cell lung cancer; HCC: Hepatocellular carcinoma; ESCC: Esophageal cell carcinoma; GC: Gastric cancer; ESCC: Esophageal squamous cell carcinoma; AML: Acute myeloid leukemia; SCLC: Small cell lung cancer; BLCA: Bladder urothelial carcinoma; BRCA: Breast invasive carcinoma; COAD: Colon adenocarcinoma; HNSC: Head and neck squamous cell carcinoma; LUAD: Lung adenocarcinoma; THCA: Carcinoma; KICH: Kidney chromophobe; KIRP: Kidney renal papillary cell carcinoma; NEIL1: NEI-like protein 1; Gabra3: Alpha-3 subunit of gamma-aminobutyric acid type A; FlNB: Filamin B; PTPN6: Protein tyrosine phosphatase non-receptor type 6; PODXL: Podocalyxin-like; GluR-B: Glutamate R-B; IGFBP7: Insulin-like growth factor-binding protein 7.

liver tissues^[90]. The same recoding editing was found in ESCC, where unlike HCC, only ADAR1 was responsible for this hyperediting. FLNB hyperediting correlated with ADAR1 levels in ESCC samples^[92]. The functional role of FLNB editing is not known.

Ras homolog family member Q (RHOQ) belongs to a family of Rho GTPases that are known to be intracellular signaling molecules regulating the actin cytoskeleton and thereby cellular functions, such as cell polarity, migration, and vesicular trafficking. Rho GTPases are present as either an active GTP-bound form or an inactive GDP-bound form^[106]. Activation of Rho GTPases is implicated in the development and progression of many types of human malignancies, including CRC^[107]. RhoQ has been most extensively studied for its central role in insulin-stimulated GLUT4 transport in adipocytes^[108]. Amino acid substitution of asparagine with serine (N136S) in the edited RhoQ was identified in colorectal cancer (CRC). The ADAR responsible has not been identified. This editing was suggested to change RhoQ protein-protein interactions and induce increased levels of RhoQ binding of GTP, causing actin cytoskeletal reorganization and increased invasion potential without affecting proliferation in CRC cell lines. Moreover, edited RHOQ was associated with recurrence of CRC when present in the tumor^[109].

Protein tyrosine phosphatase non-receptor type 6 (PTPN6) is a cytoplasmic protein expressed in hematopoietic cell development, proliferation and the receptor-mediated mitogenic signaling pathway^[110,111]. In

bone marrow mononuclear cells (BMMCs) of patients with acute myeloid leukemia, a novel PTPN6 transcript retaining intron 3 has been identified. This transcript arises from an alternative splicing reaction where editing-mediated deamination of A7866 in intron 3 erases this branch formation site, making it invisible to the splicing machinery. The ADAR responsible has not been identified. It is suggested that this retention results in the translation of a nonfunctional protein where the intron 3-encoded sequence is located in the N-terminal Src homology 2 (SH2) domain. PTPN6 binding with partner proteins, such as proto-oncogene receptor tyrosine kinase-c-Kit^[112], and its self-inhibition of phosphatase activity occurs *via* its N terminal domain^[113]. All this information suggests that its deregulation ultimately leads to uncontrolled hematopoietic growth and function. The tumor-specific editing seen in AML might correlate with the clinical course of the disease since low levels of intron-retaining transcripts in patient BMMCs at remission compared to those at diagnosis suggest that editing promotes tumorigenesis^[114].

High miRNA editing levels in cancer: ADAR1 gene amplification in NSCLC demonstrated ADAR1 overexpression in patients with early-stage lung cancer, underlining its potential oncogenic role in this cancer. Increased levels of ADAR1 corresponded with edited miR-381 levels in NSCLC. Overexpression of edited miR-381 in NSCLC possibly contributes to stemness and chemoresistance^[94].

Low editing levels in cancer

Low levels of mRNA open reading frame editing in cancer: The same correlation but in the opposite direction was shown in hypoedited cancers, such as kidney chromophobe (KICH) and kidney renal papillary cell carcinoma (KIRP), with ADAR1 mRNA paired editing levels. The ADAR2 levels checked in both studies showed a complex expression pattern but no matching editing levels (Table 1 and Figure 2)^[87,88]. The role of ADAR1 in breast cancer is not fully understood. A recent study reported high ADAR1 expression in half of the examined triple-negative-cancer patients^[115]. Conversely, it has been proposed that ADAR1 prevents tumor progression by editing the transcript coding for the alpha-3 subunit of gamma-aminobutyric acid type A (Gabra3).

The chloride-permeable gamma-aminobutyric acid type A (GABA_A) receptors are crucial mediators of fast inhibitory neurotransmission in the central nervous system^[116]. The Gabra3 transcript undergoes recoding editing of isoleucine to methionine (I/M) in the third transmembrane region. This substitution was found to affect GABA_A surface presentation and its cellular trafficking^[117]. In addition to being normally expressed in normal neuronal tissues, Gabra3 has been identified in breast cancer, where its high expression inversely correlates with breast cancer survival. ADAR1-edited Gabra3 was found in non-invasive breast cancer cell lines and was linked with the protein kinase B (Akt) pathway. A proposed mechanism for the non-invasive phenotype is that Gabra3 editing reduces its surface expression and indirectly prevents Akt activation, thereby preventing cell proliferation and invasiveness. Thus, the unedited form of Gabra3 in breast cancer is suggested to promote tumor progression, invasion and metastatic potential^[118].

Lower ADAR2 levels are recognized in gastric cancer, glioblastoma, HCC and ESCC^[91,119,120] (Figure 2). ADAR2 levels were found to correlate with changes in podocalyxin-like (PODXL) and GluR-B functions. The PODXL RNA editing event is an amino acid substitution from histidine (His) to arginine (Arg) at codon 241. This editing in the gastric cancer cell line MKN28 was shown to prevent increased growth rates and invasive capability compared to cells with the unedited form. Moreover, recoding editing of a single position located in the channel-pore-loop domain in GluR subunit B (GluR-B) (the Q/R-site) from Gln to Arg results in a channel that is impermeable to Ca²⁺^[121]. Tight regulation of editing is essential for the adequate function of this channel. Hypoedited PODXL and GluR-B with altered functions are associated with gastric cancer and malignant glioblastoma, respectively. Consequently, a tumor-suppressor role has been attributed to ADAR2^[91,119].

In ESCC, it has been reported that ADAR2 promotes apoptosis by editing and stabilizing insulin-like growth factor-binding protein 7 (IGFBP7) RNA. IGFBP7 is a secreted factor binding to and interfering with the activation of IGF1R. Through receptor occupation,

IGFBP7 blocks downstream phosphatidylinositol 3-kinase (PI3K)-AKT signaling, resulting in the inhibition of protein synthesis and cell apoptosis^[122]. IGFBP7 was previously reported to be an apoptotic promoter in prostate cancer^[123], colorectal cancer^[124] and breast cancer^[125]. The editing site in IGFBP7 is at position 284 of the coding sequence, and codon 95 is changed from AAG (lysine) to AIG, which is read as AGG (arginine) (K95R). This editing was shown to protect IGFBP7 against matriptase proteolysis in ESCC culture and xenografts, thus enabling the proapoptotic function of IGFBP7. ADAR2 is known to be downregulated in ESCC, and its upregulation induces apoptosis in ESCC cell lines *in vitro*, suggesting that IGFBP7 under editing may promote tumorigenesis in esophageal squamous cell carcinoma^[120].

Low miRNA editing levels in cancer: ADAR2 rescue in glioblastoma cells was shown to inhibit cell proliferation and migration, confirming its possible tumor-suppressor role^[126]. This anti-tumor effect might be explained through the regulation of onco-miRNAs in glioblastoma. Three particularly investigated onco-miRNAs, miR-221, miR-222 and miR-21, are overexpressed in glioblastoma^[127]. ADAR2 can edit miR-222/221 and miR-21 precursors and decrease the expression of the corresponding mature onco-miRNAs in the normal mouse brain and in different lines. Decreased levels of ADAR2 identified in glioblastoma probably push the balance of onco-miRNA/tumor-suppressor miRNA towards increased expression of onco-miRNAs, such as miR-221, miR-222 and miR-21, thereby supporting tumor progression^[128].

In the human brain, the miR-376 cluster encodes 4 pri-miRs that give rise to 5 distinct mature miRNAs, which are subjected to specific A-to-I RNA editing on 9 adenosines. In noninvasive U87 glioma cells, the expression of the unedited miR-376a* was shown to promote aggressive tumor migration and invasion of these cells both *in vitro* and *in vivo*. The editing reaction missing in the GBM cell lines generally occurs in the seed region of pri-miR-376a1 at the +9 site, ultimately giving rise to mature edited miR-376a*. The absence of this editing changes the specific targets of the miRNA. It has been identified that non edited miR-376a*, through its binding to 3' UTR, has a novel target, RAP2A, which is a member of the RAS oncogene family with an unknown function. However, the non edited miR-376a* targeting of RAP2A is unable to target the autocrine motility factor receptor (AMFR), resulting in its upregulation and possibly contributing to increased migration and invasiveness of glioma cells^[129].

Melanoma is the most aggressive type of skin cancer. It has been reported that there is a significant decrease in ADAR1 expression in approximately 65% of metastatic melanoma specimens compared to melanocytes^[130] (Table 1 and Figure 2). ADAR-1 transcripts were found to be targeted by miR-17 and miR-432, thus decreasing

ADAR1 expression. Both miR-17 and miR-432 were identified to be overexpressed in melanoma possibly due to the amplification of encoding genes^[130]. However, studies suggest that ADAR1 insufficiencies contribute to the enhancement of proliferation of melanoma cells through editing the independent regulation of miRNA biogenesis. miRNA-455-5p was identified as a target of ADAR1 in low-metastatic melanoma cells but not in highly metastatic cell lines. ADAR1 was shown to edit pri-miR-455-5p at +2 and +17 positions. This editing probably results in the reduction of the processing of pri-miRNA by Dicer or Drosha by lowering the binding affinity. However, it is also possible that ADAR1 binds to Dicer since the amount of miR-455-5p bound to Dicer and Drosha was inversely correlated with ADAR1 expression. ADAR1 was shown to form a complex with Dicer through protein-protein interactions^[131]. In this study, the authors gave a model of RNA editing in the context of melanoma progression and metastasis, where cAMP responses element binding (CREB) downregulates ADAR1 and gives rise to non-edited miR-455-5p. Expression of miR-455-5p suppresses the tumor suppressor gene cytoplasmic polyadenylation element-binding protein 1 (CPEB1), resulting in growth promotion and metastasis in melanoma cells^[132].

M5C IN CANCER RNA

Cytosine base methylation - m5C has been identified in rRNA, tRNA and recently in mRNAs and is particularly enriched in untranslated regions and near Argonaute-binding regions^[133]. The enzymes responsible for the introduction of m5C are members of the DNA methyltransferase homolog (Dnmt2) and the NOP2/Sun (NSun 2 and 4) RNA methyltransferase family^[134-136]. The role of these enzymes in the methylating activities of tumorigenesis is currently unknown. However, in circulating tumor cells from lung cancer patients, increased RNA m5C levels were shown compared to those in whole blood cells^[137]. Further investigation of the role of m5C in cancer is required.

CONCLUSION

Tight regulation of the writing, reading and eventual erasing of RNA modifications is essential for RNA metabolism. Misbalanced expression of the enzymes responsible for introducing, and in some cases removing, these modifications are considered a possible signature for specific types of cancer (Table 1). Considering the broad effect of RNA modifications on tumor cell biology, future methylome, pseudome and editome studies will shed light on those relatively unexplored epitranscriptomic mechanisms in tumors. Those studies will pave the way for the development of anti-cancer drugs that could act by steering RNA modifications.

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